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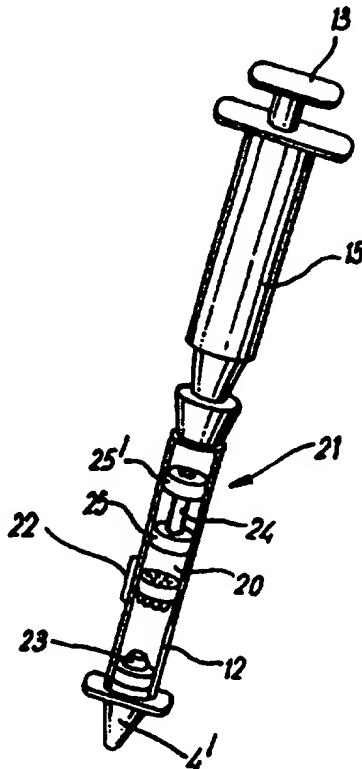
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(54) Title: FLUID SAMPLING DEVICE

(57) Abstract

There is described a device for sampling fluids, and in particular a device which can obtain a sample of body fluid such as blood, filter the sample, and perform an assay on the filtrate to detect the presence of a particular component therein. The device has filtration means (22) for separating components of the fluid, a conduit directing flow of the fluid to be sampled from a source through the device, and sensing means (21) which can detect the presence of a component in the fluid. Optionally the device has a puncture means (5), such as a hypodermic needle for puncturing the skin to access the fluid. The conduit may be a hollow fibre membrane which then also acts as the filtration means. Preferably the sensing means is also presented on a membrane surface.



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1 "FLUID SAMPLING DEVICE"

2

3 This invention relates to a device for sampling fluids,
4 and in particular concerns a device which can obtain a
5 sample of a fluid (such as blood), filter the sample,
6 and perform an assay on the filtrate to detect the
7 presence of a particular component therein, such as a
8 pathogen.

9

10 Conventional blood-sampling devices are not known to
11 comprise filter means for separating the blood
12 components before testing. Thus, to be tested for the
13 presence of viral proteins, the blood must first be
14 extracted from the patient, separated into serum and
15 cells, for example by centrifugation, and the serum
16 assayed in a separate vessel. This can be time
17 consuming and can therefore add to the costs involved
18 in a diagnostic testing procedure.

19

20 In addition, current blood sampling devices generally
21 comprise puncturing means which pierce the skin of a
22 patient and extract a relatively high volume of blood
23 from the patient, for example a needle and syringe

1 arrangement whereby the needle pierces the skin and
2 enters a blood vessel and blood is extracted from the
3 patient into the syringe body. This can be traumatic
4 for the patient and an unnecessarily high volume of
5 blood can be taken, most of which is not required for
6 sampling.

7
8 The present invention provides a device for sampling a
9 fluid, the device having filtration means for
10 separating components of the fluid, a conduit directing
11 flow of the fluid to be sampled from a source through
12 the device, and sensing means which can detect the
13 presence of a component in the fluid.

14
15 The relatively small size of the device ensures it's
16 portability and the device will normally be shaped and
17 dimensioned so to be convenient to hand-hold. The
18 device will normally be a single-use disposable item.

19
20 In certain embodiments the device has puncture means
21 such as a hypodermic needle to pierce the skin of a
22 patient and allow the sampling of blood, synovial fluid
23 or other body fluids therefrom. Biopsy needles or
24 small bore needles may be used as a puncture means in
25 the device. Fluid may also be extracted directly from
26 tissue by exerting pressure on the tissue; this
27 extraction may occur in situ or using a sample excised
28 from the patient's body.

29
30 Alternatively, the fluid may be sampled non-invasively
31 and thus a puncture means may be unnecessary. For
32 example the fluid may be tears, urine or saliva, all of
33 which can be sampled non-invasively. Thus the device
34 may have a nozzle or other means to enable access into
35 areas of restricted access.

36

1 Where present, the puncture means is desirably hollow
2 and may be linked to the conduit.

3

4 The conduit can simply comprise the filtration means in
5 the form of a hollow membrane fibre through which the
6 body fluid can flow, or a bundle of such fibres. The
7 device may also have a chamber for collecting the
8 filtrate. The chamber may also contain the sensing
9 means.

10

11 The fluid may comprise a liquid or a gas. In one
12 embodiment the fluid may be a physiological sample such
13 as blood, synovial fluid, tissue fluid, urine, tears,
14 saliva etc. The fluid may also consist of a tissue
15 sample, dissolved or suspended in a liquid medium.

16

17 However, the device may also be applied in non-medical
18 or non-veterinary applications. For example the device
19 may be used to sample fluids such as river water,
20 sewage, industrial fluids or effluent, foodstuffs (for
21 example milk, cheese, yogurt, beer, meat or fish).

22

23 Filtration of the sample preferably access through
24 cross-flow filtration

25

26 The filtration means may be woven or non-woven and can
27 optionally comprise a membrane filter having pore sizes
28 selected to separate, for example, blood cells from
29 other blood components. The filtration means can be
30 selected to filter out a particular molecule size range
31 so that only a particular size range of molecule is
32 present in the filtrate.

33

34 In one embodiment of the invention, the filtration
35 means comprises a membrane filter in the form of a
36 hollow membrane fibre or a bundle of such fibres

1 through which the body fluid flows, so that filtration
2 of the fluid occurs by cross-filtration, i.e., by flow
3 of fluid along the surface of the filtration means,
4 rather than perpendicularly towards the filtration
5 means. The filtration means can also comprise a sheet
6 of membrane filter which extends either transversely
7 across or longitudinally along the lumen of the conduit
8 or chamber, and preferably separates the needle from
9 the sensing means.

10

11 The filtration means for use in the apparatus of the
12 invention may be of any convenient shape and mention
13 may be made of hollow membrane fibres and flat sheet
14 membranes. Hollow membrane fibres or bundles of such
15 fibres may be preferred in certain situations since
16 this form permits a relatively large surface area
17 through which filtration may occur. For other
18 applications, however, flat membrane sheets (or layers
19 of such sheets) may be preferable.

20

21 The filtration means may be made of any convenient
22 material and the present invention is not limited with
23 regard to the filtration means to be used. Generally
24 the filtration means will be selected for the pore size
25 of the filter. Ceramic filters, for example, may
26 filter particles of diameter 5.0 μm to 0.1 μm and hollow
27 fibre membranes may filter molecules of 1 mDa to 5 kDa.
28 Suitable membranes are available commercially and may
29 be made of polysulphone, cellulose, cellulose
30 diacetate, polypropylene and/or ceramics materials.

31

32 In one embodiment the filtration means is in the form
33 of a membrane embedded in a holding means located
34 within the device. For example, hollow fibre
35 membranes, bent into a "U" shape, may be embedded in a
36 holder, for example a plug formed from cured adhesive.

1 The plug forms a close fit with the internal walls of a
2 conduit within the filtration device. Reference may be
3 made to the co-pending PCT Patent Application in the
4 name of FSM Technologies Ltd filed 5 December 1995,
5 claiming priority from GB9424703.8, (incorporated
6 herein by reference) as describing suitable membrane
7 filtration means.

8

9 This embodiment allows the use of a membrane having a
10 greater filtration surface area than the cross-
11 sectional filtration area of the conduit. Generally
12 the membrane in the filtration means is essentially
13 three-dimensional. The membrane may have any
14 convenient shape or configuration.

15

16 The term "cross-sectional filtration area" refers to
17 the area of a cross-section of the conduit over which
18 filtration occurs. Normally this would be the area of
19 the lumen of the conduit. It may be possible to locate
20 the filtration means part way along the length of the
21 lumen. If the walls of the conduit are sloping (and
22 therefore the cross-sectional area of the conduit
23 varies) the "cross-sectional filtration area" is the
24 cross-sectional area of the conduit at the point where
25 the filtration means is located.

26

27 It is important that part of the membrane of the
28 filtration means communicates with the exterior sides
29 of the holder so that the sample entering the device
30 (optionally under pressure) can be separated, the
31 filtrate optionally being collected in a collection
32 chamber.

33

34 In more detail the filtration means of the present
35 invention may be formed from hollow fibre membranes
36 which are wound round to form a spiral which is held in

1 a holder. The spiral may be either two dimensional,
2 that is forms a flat coil, or may be three-dimensional
3 in which case the spiral is wound upwardly into a apex.

4

5 Alternatively the filter may be formed from "U"-shaped
6 hoops of hollow membrane fibres. Preferably several
7 hoops, for example over 10 hoops, especially 20 to 50
8 hoops, are present in each filtration means. The ends
9 of each hoop pass through and are held by the holder.

10

11 The filter may be formed into hoops as described above,
12 but the upper portion of the hoops are bent into an
13 acute angle, thus forming an inverted "V" shape. The
14 angle may conveniently be introduced into the membrane
15 by spot application of heat which welds the sides of
16 the membrane together at the point where heat is
17 applied, thus forming a hinge.

18

19 In another embodiment, hollow fibre membranes each
20 having a "blind" or closed end may be used. In one
21 arrangement the blind ends may be exposed to the
22 sample. For example, multiple short lengths of hollow
23 fibres may be used, the blind end of each fibre being
24 exposed to the sample whilst the open ends are held by
25 the holder (eg are potted into the plug) and
26 communicate with the filtrate chamber. Conveniently
27 the blind ended fibres diverge away from a central
28 portion of the holder.

29

30 In an alternative embodiment using blind ended hollow
31 fibre membranes, short lengths of the fibres are cut
32 and joined together at the apex (thus closing their
33 lumens at that point) into a "teepee"-like shape. The
34 apex is exposed to the sample whilst the opposite ends
35 of the membrane fibres pass through the holder and are
36 exposed on the opposite side thereof.

1 The filtration means in this embodiment is located
2 within the device by means of the holder which will
3 normally be a plug of cured adhesive. The plug forms a
4 tight fit with the inside surfaces of the conduit
5 lumen. It is essential that the plug or any other
6 holder seals the conduit lumen, as the sample to be
7 filtered could otherwise pass through the gap between
8 the plug and the interior of the conduit. The filter
9 itself is at least partially embedded within the plug.

10
11 The plug will normally be formed from adhesive, usually
12 cured adhesive. Any material capable of forming a seal
13 with the membrane fibres and the filter chamber may be
14 used.

15
16 The adhesive used to form the filter plug of the
17 present invention may be any adhesive material which
18 does not react with the membrane or filter chamber
19 materials in a deleterious manner. Preferably the
20 adhesive material is quick setting, ie cures within
21 minutes, for example under 5 minutes. For certain
22 embodiments adhesive material which cures upon exposure
23 to light is particularly desirable. For example in
24 medical applications it may be preferred to use
25 adhesive which cures upon exposure to blue light,
26 especially UV light.

27
28 Suitable adhesive material is commercially available
29 and mention may be made of polymers available from
30 Ablestick Ltd (for example LCM 32, LCM 34 and LCM 35),
31 Bostick Ltd or Dynax Inc (eg 191M) as being suitable UV
32 curing adhesives.

33
34 The sensing means can comprise chemical agents such as
35 catalysts, pH indicators, or molecules such as DNA,
36 lectins, antibodies or abzymes (reactive against viral

1 proteins, for example) or enzymes. Alternatively, the
2 sensing means may be electronic, such as a device known
3 as an "electronic nose" which detects the presence
4 and/or concentration of a gas. Optionally, the sensing
5 means can comprise two or more of such devices and/or
6 chemicals/molecules which may act sequentially or
7 together on the same filtered sample.

8

9 The sensing means may be localised on a membrane
10 located within the device, usually so that the filtered
11 sample is exposed thereto. In one embodiment a potted
12 membrane (as described above for the filtration means)
13 is provided, the membrane being treated to allow
14 detection of a specific component that may be present
15 in the sample. Suitable examples are given in co-
16 pending PCT Patent Application No PCT/GB95/01834, the
17 disclosures of which are hereby incorporated by
18 reference.

19

20 Alternatively, the sensing means may be disposed on or
21 in the filtration means, for example, in the case of a
22 chemical or molecular sensing means, it can be bonded
23 to one side of the filter, such as by covalent or ionic
24 bonding, or by hydrophobic or hydrophilic attraction to
25 the filtration means or can be impregnated therein. It
26 may be desirable for a chemical or molecular sensing
27 means to be attached to the filtration means by
28 covalent bonding, optionally via a spacer molecule, so
29 that the presentation of the sensing means is enhanced,
30 and/or that steric interference is reduced or avoided.

31

32 Optionally, the sensing means can be provided in the
33 chamber, and can be presented on the chamber walls, or
34 on beads, rods or the like located within the chamber.

35

36 The sensing means can react with a component in the

1 filtered sample so as to effect a colour change in the
2 sensing means or in a substrate optionally present.
3 Thus, the presence/concentration of the component
4 detected can be observed visually or
5 spectrophotometrically. In such an embodiment, the
6 device or the chamber may desirably be partially or
7 wholly constructed from transparent or translucent
8 material, such as moulded plastics material.

9
10 Preferably, the puncture means comprises a needle, most
11 preferably of very narrow bore.

12
13 Embodiments of the device can provide a self contained
14 sampling and assay system, and can function effectively
15 with low volumes of fluid so as to avoid the need to
16 extract large volumes of the fluid.

17
18 The fluids to be sampled may flow into the device
19 through surface tension or capillary action without any
20 other force required to draw the body fluids towards
21 the filtration means. However, the device may be used
22 in conjunction with pressure means such as a
23 conventional syringe in order to produce a pressure
24 differential across the filtration means, for example
25 by providing a suction pressure to draw the body fluids
26 through the conduit into the device and/or across the
27 filtration means. Once the fluid has entered the
28 device, the pressurizing means may also be used to
29 induce pressure in the fluid to be filtered thereby
30 speeding up the rate of filtration. The device may
31 also incorporate sealing means to seal the fluid in the
32 device when the fluid is being pressurized, so that
33 more efficient filtration through the membrane is
34 achieved. Advantageously, the sealing means may
35 comprise a cap for the device or a portion of such a
36 cap.

1 An embodiment of the present invention will now be
2 described by way of example, with reference to the
3 accompanying drawings, in which;

4

5 Fig. 1 is a side view of a device according to the
6 invention;

7 Fig. 2 shows a detailed view of the device shown
8 in Fig. 1;

9 Fig. 3 shows the device in use drawing fluid into
10 the device;

11 Fig. 4 shows the device in use expelling fluid
12 from the syringe;

13 Fig. 5 shows a close up view of the device in use
14 drawing blood from a blood vessel into the device;

15

16 Fig. 6 shows a close up view of the device showing
17 the fluid being forced through the filtration
18 means;

19 Fig. 7 shows a cross-section an alternative device
20 according to the invention;

21 Fig. 8 shows a perspective cross-sectional view of
22 the device of Fig. 7; and

23 Fig. 9 illustrates optional attachments adapted to
24 fit onto the device of Figs. 7 and 8.

25

26 Referring now to the drawings, a device 1 according to
27 the invention comprises a needle 5 covered by a cap 6.
28 The needle 5 is hollow and its bore communicates with
29 the bore of a hollow membrane fibre 10 enclosed in a
30 housing 12 which provides support to the relatively
31 fragile membrane fibre 10. The hollow membrane fibre
32 10 is in the form of a hollow tube of exemplary
33 diameter 0.5mm formed from a membrane filter which can
34 filter out molecules of 1000kDa. One end of the fibre
35 10 is connected to the needle 5, and the other end of
36 the fibre 10 is connected to a conventional syringe 15.

1 The housing 12 comprises a hollow tube of clear
2 plastics material of internal diameter 1mm, and
3 optionally has a generally cuboidal collecting chamber
4 20 of the same material attached to one side of the
5 housing 12.

6
7 The collecting chamber 20 contains glass or plastics
8 beads (not shown) which have sensing means (in this
9 case anti-viral antibodies) attached thereto,
10 optionally by covalent bonding. The choice of sensing
11 means can vary widely according to the component to be
12 detected.

13
14 In use, the device 1 is uncapped and the needle 5 is
15 inserted into a patient's thumb (see Fig. 3) or another
16 part of the patient's body, so as to pierce a blood
17 vessel (see Fig. 5). The blood may be allowed to flow
18 through the needle 5 and hollow membrane fibre 10 by
19 capillary action or can be drawn into the device by
20 pulling the plunger 13 of the syringe 15 in the
21 direction of arrow 16 (see Fig. 3), so that blood 11 is
22 collected in the hollow membrane fibre 10. The hollow
23 membrane fibre 10 can have a very narrow bore so that
24 the volume of blood 11 required to fill it can be less
25 than 0.1 μ l.

26
27 Once a sufficient quantity of blood 11 is collected in
28 the fibre 10, the plunger 13 of the syringe may be
29 depressed in the direction of arrow 17, pressurizing
30 the blood 11 and forcing it through the membrane of the
31 fibre 10.

32
33 The cap 6 can be replaced during this step thereby
34 sealing the bore of the needle 5 at 7 and forcing the
35 blood 11 to pass through the membrane, but replacement
36 of the cap is not necessary. Sufficient pressure can

1 be obtained by depressing the syringe plunger without
2 sealing the bore. Indeed, pressurizing the blood 11 is
3 actually unnecessary since the device can simply be
4 shaken to facilitate filtration.

5

6 The blood cells and other blood components too large to
7 pass through the pores of the membrane are retained
8 within the fibre 10 and the serum containing the
9 filtered components 14 is collected in the collecting
10 chamber 20 where it mixes with the glass or plastic
11 beads to which the sensing means are attached. The
12 walls (or a portion thereof) of the chamber 20 can be
13 transparent, and a positive indication of the presence
14 of particular components can be visualised directly by
15 observing eg colour changes in a reagent optionally
16 also present in the chamber. The concentration of the
17 components can be measured by spectrophotometric
18 analysis using conventional methods.

19

20 A bulbous head 6a in the cap 6 can be used to contain
21 any fluids passing through the needle bore during the
22 pressurization step.

23

24 Modifications and improvements may be incorporated
25 without departing from the scope of the invention.
26 For example, the inner walls of the housing 12 can be
27 inclined from the chamber 20 so that all drops of
28 filtrate coming through the membrane are more
29 efficiently collected in the chamber 20. Alternatively
30 the chamber 20 may be disposed at one end of the
31 device, so that it can be shaken by hand to encourage
32 movement of drops of filtrate towards the chamber 20.

33

34 Referring to Figure 7, this shows a cross section of an
35 alternative embodiment of a device 1 according to the
36 present invention. Device 1 comprises housing 12

1 having located therein a filtration means 22 which in
2 this embodiment comprises a hollow fibre membrane
3 shaped into a "U" or hoop the ends of the fibre being
4 embedded within in a solid plug of cured adhesive so
5 that the lumen of the ends are exposed on the opposite
6 side of the plug to the main body of the "U" or hoop.
7 In use the sample enters device 1 via aperture 2, is
8 taken up into housing 12 and exposed to filtration
9 means 22. The fluid sample may be urged across the
10 filtration means 22 by application of pressure, for
11 example by fitting a conventional syringe 15 to device
12 1 as depicted in Figure 7 and urging plunger 13 of
13 syringe 15 in the direction of arrow 16. The filtrate
14 cross the hollow fibre membrane, collects in the lumen
15 thereof and passes into collection chamber 20 by
16 running down the lumen to the open ends thereof which
17 are exposed on the opposite side of the plug to the
18 main body of the hoop, facing the collection chamber
19 20. Collection chamber 20 in this embodiment is that
20 part of housing 12 located above the filtration means
21 22. The portion of the sample not able to pass through
22 the hollow fibre membrane cannot pass into the
23 collection chamber 20.

24

25 The filtrate then comes into contact with sensing means
26 21. As shown in Figure 7 sensing means 21 comprises
27 treated hollow fibre membrane 24, the ends of which
28 pass through plugs 25 and 25'. Thus, the filtrate is
29 taken into the internal lumen of hollow fibre 24, which
30 has been treated with an agent able to detect a
31 component believed to be present within the sample.
32 The presence of that component results in a colour
33 change which is directly visualised through the device,
34 for example exposing the device to UV light.

35

36 Optionally the device 1 depicted in Figure 7 may

1 comprise a puncture means 5 which in the device as
2 illustrated consists of a hypodermic needle having a
3 female luer lock 4 which engages with the male luer
4 lock 4' on the device. Once the sample is taken up
5 into device 1, puncturing means 5 may be removed and
6 disposed of for safety, to avoid the accidental
7 puncturing of the operator etc.

8

9 Figure 8 shows in more detail a perspective cross
10 sectional view of the device of Figure 7 and includes a
11 non-return valve 23 located within housing 12 to
12 prevent the inadvertent expulsion of the sample, for
13 example by depressing syringe plunger 13. In the
14 embodiment illustrated the syringe 15 is removable so
15 that device 1 can be analysed without the continued
16 presence of the syringe. Optionally a non-return valve
17 may be located at both ends of the device to prevent
18 leakage of the fluid sample.

19

20 Figure 9 illustrates alternative optional attachments
21 to device 1. Figure 9a is a biopsy needle and Figure
22 9b is a small bore needle. Both puncture means
23 illustrated in Figures 9a and 9b are provided with a
24 female luer lock 4 adapted to engage with the male luer
25 lock 4' present on device 1. As an alternative to the
26 puncture means 5, it is possible to provide a soft tip
27 fluid collection tube as illustrated in Figure 9c.
28 Again, the female luer lock 4 is adapted to engage with
29 the male luer lock 4' of device 1 in Figure 8. The
30 soft tip fluid collection tube of Figure 9c may be used
31 to facilitate collection of fluids in locations where
32 the close proximity of device 1 may be difficult, for
33 example to collect tear fluid from the eye etc.

34

35 In both Figures 7 and 8 the filtration means and
36 sensing means rely upon adhesive plugs to maintain

1 their positions within housing 12. The adhesive plugs,
2 for example formed from LCM 34 of Ablestick Ltd, form a
3 close fit with the internal surface of the lumen of
4 housing 12. Desirably housing 12 is of transparent
5 material.
6

1 CLAIMS

2

3 1. A device for sampling a fluid, the device having
4 filtration means for separating components of the
5 fluid, a conduit directing flow of the fluid
6 through the device, and sensing means which can
7 detect the presence of a component in the fluid.

8

9 2. A device as claimed in Claim 1 wherein the sensing
10 means is located to detect the presence of said
11 component in the filtered sample.

12

13 3. A device as claimed in either one of Claim 1 and 2
14 wherein the conduit is formed from a hollow fibre
15 membrane which is also the filtration means.

16

17 4. A device as claimed in either one of Claims 1 and
18 2 wherein the filtration means comprises hollow
19 fibre membrane(s) held in a plug of cured
20 adhesive.

21

22 5. A device as claimed in any one of Claim 1 to 4
23 wherein the sensing means is presented on a
24 surface of a hollow fibre membrane.

25

26 6. A device as claimed in any one of Claim 1 to 5
27 having a puncture means.

28

29 7. A device as claimed in Claim 6 wherein said
30 puncture means is a hypodermic, biopsy or small
31 bore needle.

32

33 8. A device as claimed in any one of Claims 1 to 7
34 having a pressure means.

35

36 9. A device as claimed in Claim 8 wherein said

1 pressure means is a syringe.

2

3 10. A device as claimed in any one of Claims 1 to 6
4 having a non-return valve.

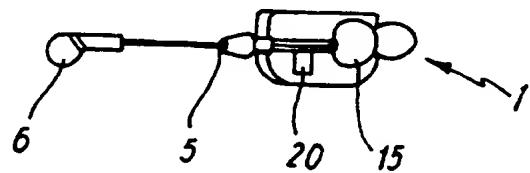


FIG. 1

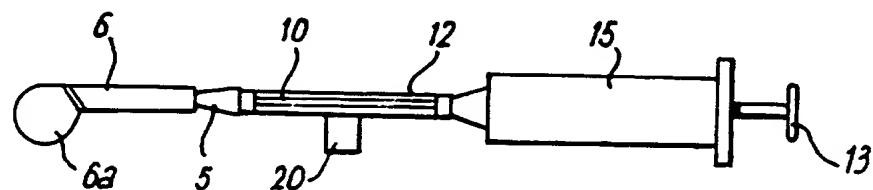


FIG. 2

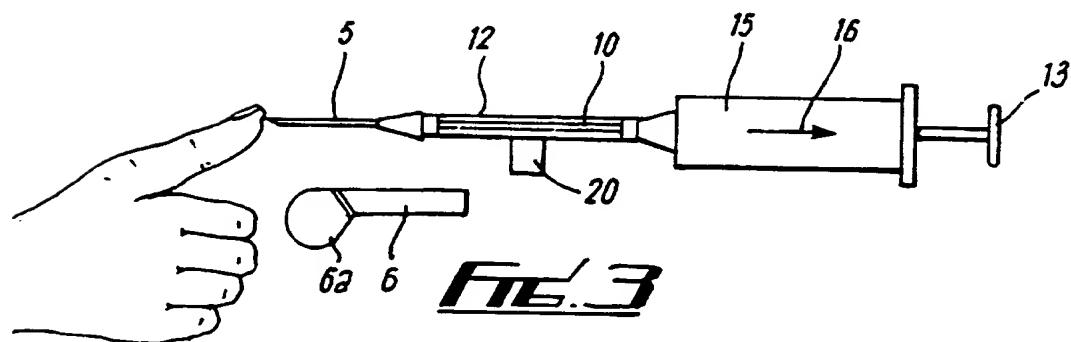


FIG. 3

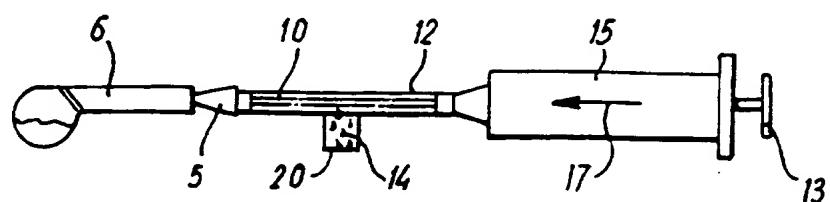


FIG. 4

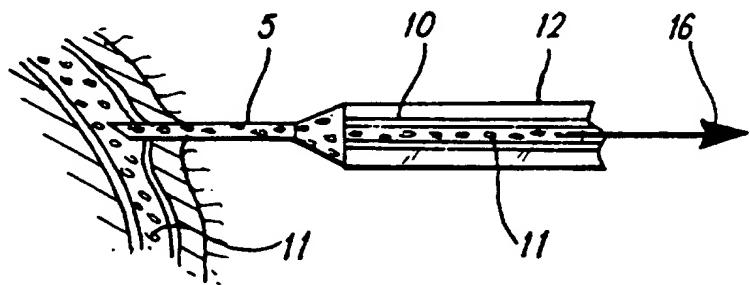


FIG. 5

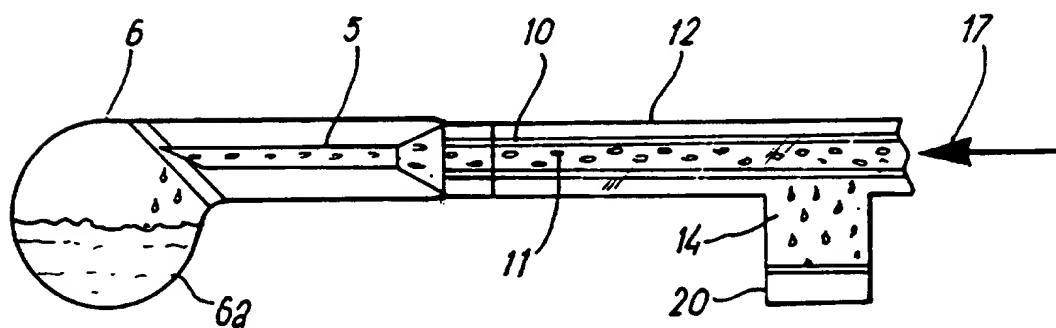


FIG. 6

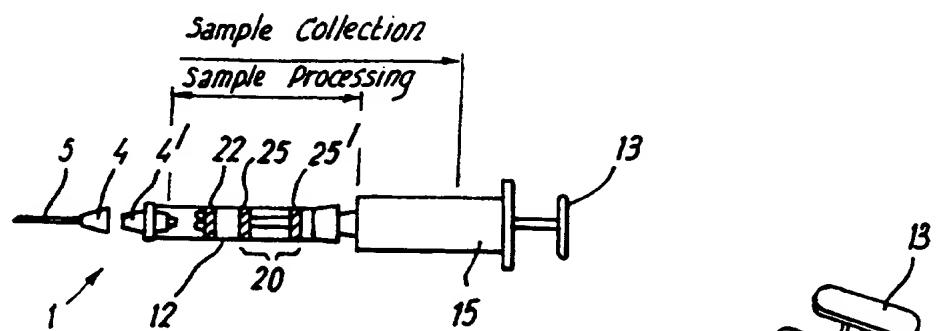


FIG. 7

FIG. 8

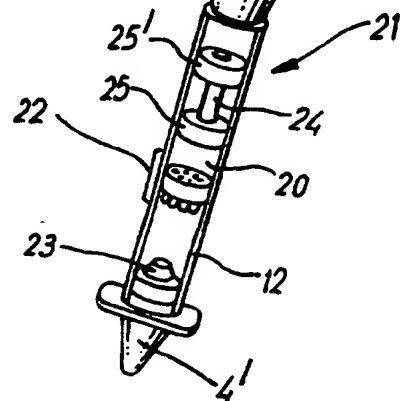
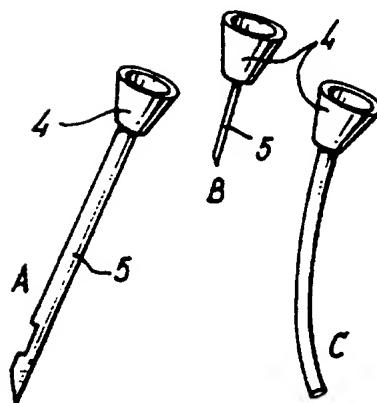


FIG. 9



INTERNATIONAL SEARCH REPORT

Int'l. Search Application No.
PCT/GB 95/03031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/49 G01N1/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 549 341 (GRACE W R & CO) 30 June 1993	1-4
Y	see column 3, line 25 - column 7, line 3	6-9
A	---	5
Y	EP,A,0 550 950 (SANWA KAGAKU KENKYUSHO CO) 14 July 1993 see abstract; figures	6-9
X	WO,A,91 08782 (PROVIVO AB) 27 June 1991 see page 8, line 7 - page 9, line 37 see page 11, line 33 - page 12, line 20	1-4,6-8, 10
A	DE,A,41 32 480 (KABE LABORTECHNIK GMBH) 8 April 1993 see abstract	8-10

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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1

Date of the actual completion of the international search 11 April 1996	Date of mailing of the international search report 26. 04. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentstaan 2 NL - 2280 HV Rijswijk Tel: (+ 31-70) 340-2040, Tx: 31 651 epo nl Fax: (+ 31-70) 340-3016	Authorized officer Bindon, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 848 580 (HYDEN V ET AL) 19 November 1974 see column 5, line 64 - column 6, line 57; figures 1,2 ---	1,2,8
A	EP,A,0 315 252 (AKZO NV) 10 May 1989 see column 3, line 30 - column 4, line 42 -----	1-3

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/03031

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-B-	6955391	18-07-91
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